

Remarks

I. Support for the Amendments

Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendments to independent claims 10-12, 18, 20 and 47 and for new claims 56-67 may be found in the originally filed claims 1, 10-12, 18, 20 and 47 and in the specification at page 10, lines 24-25; page 3, lines 5-9; page 49; page 52, lines 23-26; and Table 2. Hence, the foregoing amendments to the claims do not add new matter, and their entry into the present application is respectfully requested.

II. Information Disclosure Statement

In the Office Action at page 2, section 2, the Examiner states that the Information Disclosure Statement filed January 12, 2001, fails to comply with 37 C.F.R. § 1.98(a)(2), because copies of the cited documents are apparently unavailable. Applicants enclose a copy of the post card receipt date stamped on January 12, 2001, indicating receipt by the PTO of the subject Information Disclosure Statement with 125 documents. For the convenience of the Examiner, Applicants submit herewith copies of the 125 documents.

Applicants respectfully request that the Examiner review these documents, initial the Form PTO-1449, and return a copy to Applicants with the next Action.

III. Status of the Claims

Upon entry of the foregoing amendments, claims 10-22, 47 and 56-67 are pending in this application, with claims 10-12, 18, 20 and 47 being the independent claims.

Reconsideration of claims 10-22 and 47 is respectfully requested.

IV. Summary of the Office Action

In the Office Action dated July 24, 2001, the Examiner has made one objection to, and two rejections of, the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

V. Objection to Claims

The Examiner objected to claims 10-22 and 47 as being dependent on cancelled claims.

Claims 10, 11, 12 have now been amended to make them independent claims. Claims 18, 20 and 47 were already independent. Therefore, this objection has been accommodated, reconsideration and withdrawal of the objection are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 102(b) Over Nazarenko is Traversed

In the Office Action at pages 2-3, the Examiner has rejected claims 10-21 and 47 under 35 U.S.C. § 102(b) as being anticipated by Nazarenko *et al.*, *Nucl. Acids Res.* 25(12):2516-2521 (1997) (Doc. AR11 on the Information Disclosure Statement, filed on January 12, 2001; hereinafter "Nazarenko"). Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single enabling prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the

This requirement is not met by the disclosure of Nazarenko, which therefore cannot anticipate the invention as presently claimed.

Claims 10-12, 20 and 47 (and thus the remaining claims that depend therefrom) are drawn to methods of quantitation or detection employing oligonucleotides having a detectable label located internally. Claim 18 (and thus claims 59 and 60 that depend therefrom) is drawn to a method of amplifying a double stranded nucleic acid employing oligonucleotides having a detectable label located internally.

Nazarenko does not disclose an oligonucleotide having an internal label as suggested by the Examiner. Contrary to the Examiner's assertion, Nazarenko discloses a primer having 6-fluorescein and DABCYL at the 5'-end. See Nazarenko, p. 2517. The present application discloses that "[f]or 5'-labeled oligonucleotides, conversion from SS [single stranded] oligonucleotides to DS [double stranded] oligonucleotides caused a decrease in fluorescence, while for internally labeled oligonucleotides, conversion from SS oligonucleotides to DS caused an increase in fluorescence." See specification, at page 26, lines 11-14. Therefore, there is substantial significance in the placement of the fluorescent label in order to obtain an increase in the detectable double stranded amplified product. Hence, Nazarenko fails to disclose the invention of claims 10-12, 20 and 47 (and the claims that depend therefrom).

Nazarenko fails to expressly or inherently disclose every element of the invention as presently claimed, and therefore cannot form the basis of a rejection under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection are therefore respectfully requested.

VII. The Rejection Under 35 U.S.C. § 103(a) Over Nazarenko In View of '526 Patent

In the Office Action at pages 3-5, the Examiner has rejected claims 10-22 and 47 under 35 U.S.C. § 103(a) as being unpatentable over Nazarenko in view of Weimer *et al.*, U.S. Patent No. 6,248,526 (Doc. AD6 on the Third Supplemental Information Disclosure Statement filed on July 18, 2001; hereinafter "the '526 patent"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Moreover, there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such suggestion or motivation, the cited references may not be properly combined. *See id.* In the present case, this burden has not been met.

The invention of claims 10-12, 20 and 47 (and thus the remaining claims that depend therefrom) is drawn to methods of quantitation or detection employing oligonucleotides

having a detectable label located internally. Claim 18 (and thus claims 59 and 60 that depend therefrom) is drawn to a method of amplifying a double stranded nucleic acid employing the oligonucleotides having a detectable label located internally. Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Nazarenko. As discussed in detail above, Nazarenko does not disclose, suggest, or otherwise contemplate oligonucleotides having a detectable label positioned internally. Therefore, Nazarenko is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

The '526 patent does not cure these deficiencies of Nazarenko, since the oligonucleotides disclosed in the '526 patent are significantly different from those of the present invention: "[t]he special feature of this quenched probe system is that the fluorescence of the reporter dye (FAM), . . . is attached **to the 5' end** of the probe, is reduced by proximity to the quencher dye (TAMRA), which is attached to the 3'-end of the probe." See the '526 patent, at column 1, line 65, through column 2, line 2 (emphasis added). As noted above, the oligonucleotides used in the methods of the invention comprise a label located internally. There is absolutely no teaching or suggestion in the '526 patent to employ an oligonucleotide comprising a label located internally. Thus, the '526 patent does not cure the above-noted deficiencies of Nazarenko.

Therefore, Nazarenko and the '526 patent, when considered alone or in combination, do not disclose or suggest the methods of the present invention. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully assert that claims 10-22 and 47 are not rendered obvious by the cited art. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

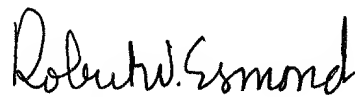
VIII. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

- (a) Claims 1-9, 23-46, and 48-55 have been cancelled.
- (b) New claims 56-67 are sought to be added.
- (c) Claims 10-12, 18, 20 and 47 are amended as follows:

10. (Once amended) A method for the quantification or detection of one or more target nucleic acid molecules in a sample comprising hybridizing one or more detectably labeled oligonucleotides [of claim 1] with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule, and detecting the presence or absence and/or quantifying the amount of said one or more target nucleic acid molecules.

11. (Once amended) A method for the quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid synthesis comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides [of claim 1], wherein said one or more oligonucleotides comprise one or more detectable labels located internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule;

incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to all or a portion of said one or more templates, said one

or more synthesized nucleic acid molecules comprising said one or more oligonucleotides;
and

detecting the presence or absence or quantifying the amount of said one or more synthesized nucleic acid molecules by measuring said one or more detectable labels.

12. (Once amended) A method for quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid amplification comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides [of claim 1] under conditions sufficient to amplify one or more nucleic acid molecules complementary to all or a portion of said one or more templates, said one or more amplified nucleic acid molecules comprising said one or more oligonucleotides, wherein said one or more oligonucleotides comprise one or more detectable labels located internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule; and

detecting the presence or absence or quantifying the amount of said one or more nucleic acid molecules by measuring the detectable labels of said oligonucleotides.

18. (Once amended) A method for amplifying a double stranded nucleic acid molecule, comprising:

providing a first and second primer, wherein said first primer is complementary to a sequence within or at or near the 3'-termini of the first strand of said nucleic molecule and said second primer is complementary to a sequence within or at or near the 3'-termini of the second strand of said nucleic acid molecule;

hybridizing said first primer to said first strand and said second primer to said second

strand in the presence of one or more [of the] polymerases, under conditions such that a third nucleic acid molecule complementary to all or a portion of said first strand and a fourth nucleic acid molecule complementary to all or a portion said second strand are synthesized;

denaturing said first and third strands, and said second and fourth strands; and

repeating the above steps one or more times, wherein one or more of the primers comprise [a] one or more detectable labels located internally [and/or at or near its 3' and/or 5' termini and/or comprises one or more hairpin structures].

20. (Once amended) A method for the quantification or detection of nucleic acids molecules comprising:

mixing one or more labeled oligonucleotides with one or more nucleic acid molecules to be detected or quantitated, wherein said one or more oligonucleotides comprise one or more detectable labels located internally; and

detecting or measuring an increase in fluorescence associated with said one or more oligonucleotides hybridizing to said one or more nucleic acid molecules.

47. (Once amended) A method for detecting a target nucleic acid sequence, comprising:

contacting a sample containing a mixture of nucleic acid molecules with at least one oligonucleotide[, the oligonucleotide] capable of hybridizing with a target nucleic acid molecule and compris[es]ing a detectable moiety located internally, wherein the detectable moiety undergoes a change in one or more observable propert[y]ies upon hybridization to the target nucleic acid molecule; and

observing the observable property, wherein a change in the observable property